

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

REC'D 30 MAR 2006

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To:

see form PCT/ISA/220

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY  
(PCT Rule 43bis.1)

Date of mailing

(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference

see form PCT/ISA/220

**FOR FURTHER ACTION**

See paragraph 2 below

International application No.

PCT/L2005/000754

International filing date (day/month/year)

14.07.2005

Priority date (day/month/year)

15.07.2004

International Patent Classification (IPC) or both national classification and IPC

INV. A61K45/00 A61K38/05 A61K38/06 A61K38/07 A61K31/34 A61K31/38 A61K31/385 A61K31/39 A61K31/40

Applicant

RAMOT AT TEL AVIV UNIVERSITY LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
Fax: +49 89 2399 - 4465

Authorized Officer

Böhrerova, E

Telephone No. +49 89 2399-7859



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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:
    - ☒ a sequence listing
    - ☐ table(s) related to the sequence listing
  - b. format of material:
    - ☒ in written format
    - ☒ in computer readable form
  - c. time of filing/furnishing:
    - ☒ contained in the international application as filed.
    - ☐ filed together with the international application in computer readable form.
    - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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**Box No. II Priority**

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1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 1 (completely), 8-30 (partially)

because:

- ☒ the said international application, or the said claims Nos. 1 (completely), 8-30 (partially) relate to the following subject matter which does not require an international preliminary examination (*specify*):  
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
  - the written form ☐ has not been furnished
  - ☐ does not comply with the standard
  - the computer readable form ☐ has not been furnished
  - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

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**Box No. IV Lack of unity of invention**

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1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
- ☒ paid additional fees.
  - ☐ paid additional fees under protest.
  - ☐ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
  - ☒ not complied with for the following reasons:  
    **see separate sheet**
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
  - ☐ the parts relating to claims Nos.

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**Box No. V Reasoned statement under Rule 43b/s.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	3,12,16-30
	No: Claims	1,2,4-11,13-15,31-59
Inventive step (IS)	Yes: Claims	-
	No: Claims	1-59
Industrial applicability (IA)	Yes: Claims	2-7
	No: Claims	-

2. Citations and explanations

**see separate sheet**

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**Box No. VIII Certain observations on the international application**

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The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

technical feature novel and inventive over the prior art and the application, hence does not meet the requirements of unity of invention as defined in Rules 13.1 and 13.2 PCT.

**Cited documents**

Reference is made to the following documents:

- D1: DE 100 43 282 A1 (HEININGER, KURT) 28 March 2002
- D2: FORLONI A G ET AL: "Anti-amyloidogenic activity of tetracyclines: studies in vitro" FEBS LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 487, no. 3, 5 January 2001, pages 404-407
- D3: WO 01/10457 A (TRIEPE AB; VAHLNE, ANDERS) 15 February 2001
- D4: EP-A-0 081 122 (HELOPHARM W. PETRIK & CO.KG) 15 June 1983
- D5: DE 34 12 445 A1 (MEYER-GLAUNER, WILHELM, DR; MEYER-GLAUNER, WILHELM, DR., 7400 TUEBINGEN,) 10 October 1985
- D6: WO 80/00789 A (ABBOTT LABOR) 1 May 1980
- D7: LANSBURY P T JR: "Following nature's anti-amyloid strategy." NATURE BIOTECHNOLOGY, vol. 19, no. 2, February 2001, pages 112-113
- D8: GRATEAU GILLES: "[Coli's curli or how amyloid can be physiological.]" M-S (MEDECINE SCIENCES), vol. 18, no. 6-7, 2002, page 664
- D9: CHERNY IZHACK ET AL: "The formation of curli amyloid fibrils is mediated by prion-like peptide repeats." BIOPHYSICAL JOURNAL, vol. 86, no. 1, January 2004, page 508a, XP009057812 & 48TH ANNUAL MEETING OF THE BIOPHYSICAL SOCIETY; BALTIMORE, MD, USA; FEBRUARY 14-18, 2004
- D10: US-A-4 626 540 (CAPPS ET AL) 2 December 1986
- D11: US 2003/225155 A1 (FERNANDEZ-POL JOSE A ET AL) 4 December 2003
- D12: WO 01/45726 A (MARS, INCORPORATED; SCHMITZ, HAROLD, H) 28 June 2001
- D13: US-A-4 970 233 (MCHUGH ET AL) 13 November 1990
- D14: DATABASE WPI Section Ch, Week 199104 Derwent Publications Ltd., London, GB; Class B02, AN 1991-025973 & JP 02 295923 A (TAIYO CHEM IND CO LTD) 6 December 1990
- D15: PATENT ABSTRACTS OF JAPAN vol. 008, no. 134 (C-230), 21 June 1984 & JP 59 044313 A (YAKULT HONSHA KK), 12 March 1984
- D16: US-B1-6 593 339 (EEK ARNE ET AL) 15 July 2003
- D17: INGLOT A D: "Comparison of the antiviral activity in vitro of some non-steroidal

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AUTHORITY (SEPARATE SHEET)**

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anti-inflammatory drugs" JOURNAL OF GENERAL VIROLOGY, SOCIETY FOR  
GENERAL MICROBIOLOGY, SPENCERS WOOD, GB, vol. 4, no. 2, March 1969,  
pages 203-214

- D18: WO 03/077866 A (ASH MEDICAL SYSTEMS, INC; ASH, STEPHEN, R;  
STECZKO, JANUSZ) 25 September 2003
- D19: DATABASE WPI Section Ch, Week 198515 Derwent Publications Ltd., London,  
GB; Class A96, AN 1985-090446 & JP 60 040061 A (UNITIKA LTD) 2 March 1985
- D20: PAVIA CHARLES S ET AL: "Antimicrobial activity of nicotine against a spectrum of  
bacterial and fungal pathogens" JOURNAL OF MEDICAL MICROBIOLOGY, vol.  
49, no. 7, July 2000 (2000-07), pages 675-676
- D21: WO 97/16191 A (WARNER-LAMBERT COMPANY; HAYS, SHERYL, JEANNE;  
LEVINE, HARRY, III;) 9 May 1997

Unless indicated otherwise reference is made to the passages considered relevant in the  
search report.

**Re-Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**First invention (proteinaceous agents)**

**Novelty**

The subject-matter of claims 1,2,4-11,13-15 is considered to lack novelty in terms of Art. 33(1) and (2) PCT.

As already stated above (see part Unity), novelty of claims 1 and 2 is anticipated by the disclosure of D1 and D2.

D3 features small peptides that modulate the protein-protein interactions necessary for protein polymerization and the assembly of supramolecular protein complexes. The disclosed peptides inhibit polymerization of beta amyloid (i.e. they are anti-amyloid agent), viral capsid protein, and bacterial toxins. They are used for the treatment of viral diseases and bacterial infections. The peptides are further used for coating of medical devices, preferably condoms and gloves. This disclosure anticipates novelty of claims 1,2,5-8,10,11.

D4 teaches carrier tripeptides of the general formula L-Arg-X-L-Phe, wherein X is an atypical amino acid with a substituted phenyl. The tripeptides exhibit antifungal activity. This disclosure is considered to anticipate novelty of claims 1,2,9-11,13-15. D5 discloses an antifungal tripeptide L-Arg-tert.-butyl-DL-glycyl-L-phenylalanine. This disclosure is prejudicial to novelty of claims 1,2,9-11,13-15.

D5 discloses peptides with antibacterial activity. At least some of the preferred peptides (e.g. L-Phe- $\beta$ F-D-Ala) fall within the scope of the general formula X-Y defined by present claim 13. Consequently, the disclosure of D6 is considered to anticipate novelty of claims 1,2,8,10,11,13-15.

It is to be stressed that the fact that present claims define the peptides as anti-amyloid agents and that D4 - D6 are silent about an anti-amyloid activity of the disclosed peptides

cannot confer novelty to the subject-matter of the claims concerned. According to the practice of this Authority, discovery of a new mechanism of action of an active agent cannot confer novelty to a claim if the same active agent is claimed for the same medical use as disclosed in the prior art. In this respect, it is considered that the knowledge of the anti-amyloid activity of the peptides of D4-D6 would not anyhow change the way a medical practitioner uses them in the treatment of pathogen infections as known from D4-D6.

Novelty of claim 4 is anticipated by the disclosure of D7 teaching an assay for identifying small-molecule inhibitors of amyloid beta aggregation based on the observation of beta-galactosidase generation in the *E. coli* cytoplasm by complementation of two fragments. By fusing one of these fragments to the C terminus of amyloid beta protein, the generation of functional beta-galactosidase is dependent on the solubility of the fusion protein. Thus, the aggregation of amyloid beta produces inactive beta-galactosidase, but a drug-like small molecule may be able to restore the activity of the fusion. The disclosed assay comprises all the features of claim 4, namely the steps of contacting molecules with an amyloid forming pathogen (*E. coli*) and identifying molecules capable of altering amyloid formation by said pathogen.

The subject-matter of claims 3, 12, 16-30 is considered to be novel in terms of Art. 33(1) and (2) PCT.

### **Inventive step**

As the subject-matter of claims 1,2,4-11,13-15 lacks novelty, no inventiveness can be acknowledged.

In case novelty of claim 4 over the disclosure of D7 is to be acknowledged, it would be considered to lack an inventive step over the disclosure of D7 and D8.

The subject-matter of claims 16-30 is considered to lack an inventive step under Art. 33(1) and (3) PCT since evidence that the problem to be solved - provision of an agent for the treatment of pathogen infection - has indeed been solved throughout the whole scope claimed is lacking. The experimental data present in the application show that peptides

SEQ ID NOs. 9, 10, and 11 inhibit curli formation by *E. coli*.

Firstly, the peptides SEQ ID NOs 9-11 all comprise a common oligopeptide QFGGGNP, thus it is considered that this oligopeptide is necessary in order to achieve the claimed effect. The application provides no proof that any an oligopeptide being 2-15 amino acids in length and comprising an amino acid sequence YX or YX, as presently claimed by claims 13-30, would exhibit the same biological effect.

Secondly, although the experimental data present in the application prove that oligopeptides SEQ ID NO. 9,10,11 indeed inhibit curli formation of *E. coli*, there is reasonable doubt that they would be effective in the treatment of any pathogen infection, especially infections by pathogens which do not produce amyloid-like aggregates.

Thirdly, the aggregation of amyloid-like structures is known to play role in the formation of biofilms by pathogenic microorganisms producing amyloid-like proteins, therefore it can be admitted that inhibitors of the aggregation can prevent formation of such biofilms. However, no connection between the biofilm formation and a systemic pathogen infection is apparent. Consequently, it is not sufficiently proven that the inhibitors of biofilm formation would be indeed effective in the treatment of systemic pathogen infections.

As the technical problem has not been solved throughout the whole scope claimed, no inventiveness can be acknowledged.

Furthermore, the data present in the application appear to be obvious on the base of D9 teaching that *E. coli* curli protein forms amyloid structures and that the conjugation of beta-breaker elements to the prion-like repeat significantly inhibits the formation of amyloid by curli expressing bacteria.

### **Industrial applicability**

Subject-matter of claims 2-7 is considered to be industrially applicable under Art. 33(1) and (4) PCT.

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For the assessment of independent claim 1 and claims 8-30 dependent thereon on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**Second invention (non-proteinaceous agents)**

**Novelty and Inventive step**

The subject-matter of claims 1,2,5-9,31-59 is considered to lack novelty in terms of Art. 33(1) and (2) PCT as being anticipated by the disclosure of D1, D2, D10-D20.

D1 discloses the use of agents inhibiting amyloid formation and/or secretion, including agents falling within the scope of the general formula of claim 41, for the treatment of variety of disorders including infection diseases.

D2 teaches that tetracycline and doxycycline, classical antibiotics (i.e. anti-infective agents) exhibit anti-amyloidogenic activity, thus that agents with anti-amyloidogenic activity are used as antibiotics.

D10 disclose the use of substituted 1-amino-4-nitroacridinones for the treatment of bacterial infections.

D11 discloses the use of specific metal chelating agents including furoic acid, 2-thiophenecarboxylic acid and their derivatives for the treatment of viral, bacterial or parasitic infections.

D12 teaches the use of procyanidin for the treatment or prevention of viral infection.

D13 discloses that phenolphthalein is an effective treatment for the viral infections of AIDS.

D14 features compositions for inhibiting Clostridium infection comprising catechin, epicatechin, gallo catechin, epigallocatechin, epicatechin gallate, and epigallocatechin gallate as active ingredients.

D15 discloses an antibacterial composition comprising quercetin as the active component.

D16 features the use of NO-releasing NSAIDs for the treatment of bacterial infections, especially caused by Helicobacter pylori.

D17 teaches the in vitro anti-viral activity of several NSAIDs.

D18 discloses antimicrobial activity of organic dyes including methylene blue, acridine orange, etc. It further features medical devices for implantation comprising a polymeric material impregnated with an organic dye exhibiting antibacterial activity.

D19 features an urethral catheter with incorporated acridine or its salt as an antibacterial substance.

D20 teaches antimicrobial activity of nicotine.

Present claims are directed to a method of treatment of a pathogen infection by administering an non-proteinaceous anti-amyloid agent. At least some of the agents used in D1, D2, D10-20 are known to possess anti-amyloid activity: for D1 and D2 see part Unity, the anti-amyloid activity of nitroacridinones used in D10 is known from D21, and the anti-amyloid activity of chelating agents of D11 is disclosed therein (see paragraphs 440-453 of D11).

However, even if the used agents are not known to have the anti-amyloid activity, the disclosure of the cited documents anticipates novelty of the present claims as the same agents are used for the treatment of the same disorders (pathogen infection) as presently claimed. The fact that the application defines the known anti-infective agents as "anti-amyloid" cannot convey novelty to the claims directed to the use of the same agents for treating the same disorders. According to the practice of this Authority, discovery of a new mechanism of action of an active agent cannot confer novelty to a claim if the same active agent is claimed for the same medical use as disclosed in the prior art. In this respect, it is considered that the knowledge of the anti-amyloid activity of the agents of D1, D2, D10-D20 would not anyhow change the way a medical practitioner uses them in the treatment of pathogen infections.

If novelty of some of the claims 1,2,5-9,31-59 over D1, D2, D10-D20 was acknowledged an objection of lack of inventive step in terms of Art. 33(1) and (3) would be raised. It is to be stressed that the application does not provide any experimental data concerning non-proteinaceous agents as presently claimed. Thus, it is to be stated that no technical effect of the claimed compound over the prior art is apparent and that it was not proven that the claimed solution actually solves the technical problem posed. Consequently, no inventiveness could be acknowledged.

### **Industrial applicability**

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Subject-matter of claims 2, 5-7 is considered to be industrially applicable under Art. 33(1) and (4) PCT.

For the assessment of independent claim 1 and claims 8,9,31-59 dependent thereon on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Re Item VIII**

**Certain observation on the international application (clarity)**

Present claims 1-9 encompass compounds defined only by their desired function (anti amyloid agents), contrary to the requirements of support and disclosure in the sense of Article 6 and 5 PCT. The fact that any compound could be screened does not overcome this objection, as the skilled person would not have a knowledge beforehand as to whether it would fall within the scope claimed. Undue experimentation would be required to randomly screen compounds for their anti-amyloid activity.

Claim 3 is directed to a method of typing a pathogen comprising monitoring an alteration in growth and/or infectivity of the pathogen in the presence of an anti-amyloid agent. However, neither the claim, nor the specification define further steps necessary to perform the typing of a pathogen, i.e. how results of the growth and/or infectivity monitoring define a concrete type of a pathogen. The application lacks disclosure in such an extent that a person skilled in the art would not be able to carry out the claimed method, i.e. to type an pathogen by the method claimed.

Claims 8-59 are formulated as directed to the method, use and medical device according to previous claims which renders the category (method, use, or product) and therefore the scope of protection of these claims unclear.

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**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Independent claim 1 and claims 8-30 dependent thereon relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item IV**  
**Unity**

The problem to be solved by the present application can be defined as to provide an agent for preventing or treating a pathogen infection in a subject. The solution as proposed by independent claims 1 and 2 is the use of an anti-amyloid agent.

However, the subject-matter of independent claims 1 and 2 is already known from the prior art. D1 discloses use of agents inhibiting amyloid formation and/or secretion for the treatment of variety of disorders including infection diseases. D2 teaches that tetracycline and doxycycline, classical antibiotics (i.e. anti-infective agents) exhibit anti-amyloidogenic activity, thus that agents with anti-amyloidogenic activity are used as antibiotics. The requisite unity of invention (Rule 13.1 PCT) therefore no longer exists inasmuch as a technical relationship involving one or more of the same or corresponding special technical features in the sense of Rule 13.2 PCT does not exist between the subject-matter of the following groups of dependent claims:

1. Claims 10-30 directed to a method, use or a medical device wherein said anti-amyloid agent is a proteinaceous agent;
2. Claims 31-59 directed to a method, use or a medical device wherein said anti-amyloid agent is a non-proteinaceous agent.

Consequently, this Authority considers that there are 2 inventions covered by the claims indicated as follows:

I: Claims 1, 2, 5-9 (all partially) and 3, 4, 10-30 directed to a method of preventing or treating a pathogen infection in a subject by administering a proteinaceous anti-amyloid agent, a corresponding medical use, a medical device comprising a proteinaceous anti-amyloid agent attached thereto, a method of typing a pathogen, and a method of identifying an anti-amyloid agent.

II: Claims 1, 2, 5-9 (all partially), and 31-59 directed to a method of preventing or treating a pathogen infection in a subject by administering a non-proteinaceous anti-amyloid agent, a corresponding medical use, and a medical device comprising a non-proteinaceous anti-amyloid agent attached thereto.

In conclusion, the groups of claims are not linked by common or corresponding special